Well-differentiated hepatocellular lesions
Evidence-based Immunohistochemical Panels

Sanjay Kakar, MD
University of California, San Francisco
Outline

Hepatocellular adenoma
  • WHO Classification
  • Role of Immunohistochemistry
    Diagnosis of histologic subtypes
    Distinction from HCC and FNH
Hepatocellular adenoma

A story of two revolutions
American Revolution

French Revolution
Oral contraceptives and HCA

Janet Baum, MD
Dept of Radiology
Beth Israel, Harvard Univ
Journal reviews

JAMA
New England Journal of Medicine
Radiology

Rejected with ridicule
Possible association between benign hepatomas and oral contraceptives.

Baum JK, Bookstein JJ, Holtz F, Klein EW.

Abstract

7 case reports of women with benign hepatic adenoma suggest that, since all of the women were taking oral contraceptives (OCs), there may be an association between ingestion of exogenous hormones and development of benign hepatoma of the liver. The cases were rapidly diagnosed by using hepatic arteriography; prompt, precise diagnosis is emphasized because, though the tumors are benign, they may cause serious, if not fatal, hemorrhage if left unchecked. Case 1 was a 26-year-old woman who had taken Enovid for 2 years, who presented with acute abdomen and impending shock. Coliotomy was performed, in which a left-lobe hepatic tumor was found; she underwent left heptectomy and cholecystectomy and no evidence of recurrence was found 1 year later. Case 2 had been taking Oracon for a unknown time. Case 3, on OCs for 6 years, had a pedunculated mobile tumor removed. Case 4, 25 years old, had been taking Ovaral for 6 months before diagnosis and excision of a right lobe liver tumor. Case 5, 5 years on combined OCs, required surgical intervention for a hypervascular mass. Case 6, taking a total of 8 years of OC therapy, was operated on for an hepatic mass which was a white-to-yellow hemorrhagic mass. Case 7, taking Enovid for 7 years, yielded a surgical specimen that was hemorrhagic, partly necrotic, and yellow-tan, about 10 cm in diameter.
February 19, 1975

Janet K. Baum, M.D.
Department of Radiology
University Hospital
University of Michigan
Ann Arbor, Michigan 48104

Re: Ms. #13353, "Liver Tumors and Oral Contraceptives," Baum et al; and
Ms. #13307, "Liver Cell Adenoma and Oral Contraceptives," Antoniades

Dear Doctor Baum:

The Journal will be pleased (even with some embarrassment) to publish your letter in a future issue. Evidently, some editors of The Journal missed the boat about five years ago--but I must admit that any of us may do so sometimes.

I have changed the wording slightly at one point: I do not believe we can confidently say that Dr. Mays made no mention of your article. It is possible that he did so and the Medical News reporter just didn't record the fact.
Hepatocellular adenoma

The French Revolution
# HCA: genetic classification

<table>
<thead>
<tr>
<th>Genetic Classification</th>
<th>Gene/Pathway Related</th>
</tr>
</thead>
<tbody>
<tr>
<td>HNF-1α inactivation</td>
<td><em>TCF1</em> gene that encodes hepatocyte nuclear factor</td>
</tr>
<tr>
<td>β-catenin activation</td>
<td><em>CTTNB1</em> exon 3 mutation (encodes β-catenin)</td>
</tr>
<tr>
<td>IL-6 pathway activated (Inflammatory)</td>
<td><em>IL6R</em> gene (encodes gp130), <em>FRK</em>, <em>STAT3</em>, <em>GNAS</em></td>
</tr>
<tr>
<td>Mutation-negative</td>
<td>No <em>HNF-1α</em> or β-catenin mutation</td>
</tr>
</tbody>
</table>

Zucman-Rossi, Hepatology, 2006
WHO blue book, 2010
## HCA subtypes

<table>
<thead>
<tr>
<th></th>
<th>HNF1α-mutated</th>
<th>β-catenin mutated</th>
<th>Inflammatory</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong></td>
<td>~90%</td>
<td>~60%</td>
<td>~90%</td>
</tr>
<tr>
<td><strong>Histologic features</strong></td>
<td>Steatosis</td>
<td>Cytologic</td>
<td>Sinusoidal dilatation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>abnormalities</td>
<td>Inflammation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ductular reaction</td>
</tr>
<tr>
<td><strong>Association with HCC</strong></td>
<td>Rare</td>
<td>40%</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

- **Steatosis**: Fat accumulation in liver cells.
- **Cytologic abnormalities**: Abnormal cell morphology.
- **Sinusoidal dilatation**: Expansion of the space between liver cells.
- **Inflammation**: Presence of immune cells.
- **Ductular reaction**: Stimulation of bile duct growth.
## HCA: immunohistochemistry

<table>
<thead>
<tr>
<th>HNF-1α mutated</th>
<th>β-catenin mutated</th>
<th>Inflammatory</th>
<th>Unclassified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver fatty acid binding protein (LFABP)</td>
<td>β-catenin</td>
<td>C reactive protein (CRP)</td>
<td>No defining features</td>
</tr>
<tr>
<td>-Glutamine synthetase (GS)</td>
<td>CRP+</td>
<td>Serum amyloid associated protein (SAA)</td>
<td></td>
</tr>
<tr>
<td>Unclassified</td>
<td>Nuclear β-catenin Diffuse GS</td>
<td>SAA+</td>
<td></td>
</tr>
</tbody>
</table>

Bioulac-Sage, Hepatology 2007
HNF1α mutated (H-HCA)

- Women
- Steatosis
- Atypia, risk of HCC: minimal
- Fatty acid binding protein absent
FNH with fat
<table>
<thead>
<tr>
<th>HNF1-mutated</th>
<th>Beta-catenin mutated (exon 3)</th>
<th>Inflammatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatty acid binding protein (FABP)</td>
<td>-Beta-catenin&lt;br&gt;-Glutamine synthetase (GS)</td>
<td>-C reactive protein (CRP)&lt;br&gt;-Serum amyloid associated protein (SAA)</td>
</tr>
<tr>
<td>FABP negative</td>
<td>Nuclear beta-catenin&lt;br&gt;Diffuse GS</td>
<td>CRP+&lt;br&gt;SAA+</td>
</tr>
</tbody>
</table>
Inflammatory hepatocellular adenoma (I-HCA)

- Inflammation
- Sinusoidal dilatation
- Ductular reaction
SAA in inflammatory adenoma
## HCA: immunohistochemistry

<table>
<thead>
<tr>
<th>HNF-1α mutated</th>
<th>β-catenin mutated</th>
<th>Inflammatory</th>
<th>Unclassified</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Fatty acid binding protein (FABP)</td>
<td><strong>β-catenin</strong> Glutamine synthetase (GS)</td>
<td>- C reactive protein (CRP)</td>
<td>No defining features</td>
</tr>
<tr>
<td>FABP negative</td>
<td><strong>Nuclear β-catenin</strong> Diffuse GS</td>
<td>- Serum amyloid associated protein (SAA)</td>
<td>CRP+ SAA+</td>
</tr>
</tbody>
</table>
β-catenin mutated, exon 3 (b-HCA)

- 40% men
- Cytologic atypia, frequent association with HCC
- Nuclear translocation of β-catenin
Normal liver: perivenular GS

β-catenin-activation: diffuse GS
<table>
<thead>
<tr>
<th></th>
<th>HNF-1α inactivated</th>
<th>Inflammatory</th>
<th>β-catenin activated</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>35-50%</td>
<td>40-50%</td>
<td>10%</td>
</tr>
<tr>
<td>Sex and OC use</td>
<td>Women, OC use</td>
<td>Women (OCs), men</td>
<td>40% in men</td>
</tr>
<tr>
<td></td>
<td>Obesity, diabetes</td>
<td></td>
<td>Androgens, glycogen storage disease</td>
</tr>
<tr>
<td></td>
<td>Marked steatosis, no atypia</td>
<td>Inflammation, sinusoidal dilatation, ductular reaction</td>
<td>Pseudoacinar, small cell change</td>
</tr>
<tr>
<td></td>
<td>HCC rare</td>
<td>HCC rare</td>
<td>HCC 40%</td>
</tr>
<tr>
<td></td>
<td>LFABP negative</td>
<td>SAA positive</td>
<td>Nuclear β-catenin Diffuse GS</td>
</tr>
<tr>
<td></td>
<td>CRP positive</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Unclassified (5-10%): no known defining features
Practical considerations

- Are all stains necessary for clinical care?
- Is it necessary to determine subtype of HCA?
- What is the significance of β-catenin activation?
Case 1

- 32 year old woman on OCs
- Ultrasound for workup of abdominal pain
- 5 cm liver mass, suggestive of FNH on imaging
- Inflammation
- Arterioles
- Few ductules
- Sinusoidal dilatation
## FNH vs. HCA

<table>
<thead>
<tr>
<th></th>
<th>Focal nodular hyperplasia</th>
<th>Hepatocellular adenoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clonality</strong></td>
<td>Polyclonal</td>
<td>Monoclonal</td>
</tr>
<tr>
<td><strong>Resection</strong></td>
<td>Not required except when symptomatic</td>
<td>Most cases (&gt;5 cm, male gender)</td>
</tr>
</tbody>
</table>
### FNH vs. HCA

<table>
<thead>
<tr>
<th></th>
<th>Focal nodular hyperplasia</th>
<th>Hepatocellular adenoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central scar</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Fibrous septa</td>
<td>Typically present</td>
<td>Typically absent</td>
</tr>
<tr>
<td>Nodular architecture</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Ductular reaction</td>
<td>Generally prominent</td>
<td>Absent</td>
</tr>
<tr>
<td>Histologic feature</td>
<td>FNH</td>
<td>Inflammatory HCA</td>
</tr>
<tr>
<td>--------------------------</td>
<td>------</td>
<td>------------------</td>
</tr>
<tr>
<td>Fibrous bands</td>
<td>90%</td>
<td>26%</td>
</tr>
<tr>
<td>Ductular reaction</td>
<td>83%</td>
<td>43%</td>
</tr>
<tr>
<td>Sinusoidal dilatation</td>
<td>18%</td>
<td>83%</td>
</tr>
<tr>
<td>Inflammation</td>
<td>40%</td>
<td>60%</td>
</tr>
<tr>
<td>Steatosis</td>
<td>21%</td>
<td>57%</td>
</tr>
</tbody>
</table>

Joseph/Kakar, Mod Pathol 2014
## FNH or inflammatory HCA

<table>
<thead>
<tr>
<th>Immunostain</th>
<th>Inflammatory HCA</th>
<th>FNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum amyloid A (SAA)</td>
<td>Moderate to strong</td>
<td>Absent/focal</td>
</tr>
<tr>
<td>Glutamine synthetase (GS)</td>
<td>β-catenin activated: diffuse</td>
<td>Map-like</td>
</tr>
<tr>
<td></td>
<td>Others: Perivascular/patchy</td>
<td></td>
</tr>
</tbody>
</table>
GS: map-like pattern, typical of FNH
GS: patchy staining ± perivascular staining
Most HCA (without β-catenin activation)
Case 1: FNH with telangiectasia

- Map-like GS pattern
- SAA negative
Case 2: 40/F, biopsy from a 4 cm liver mass
Inflammatory HCA

GS: negative

SAA: positive
# Two stain approach: FNH vs I-HCA

<table>
<thead>
<tr>
<th>Stain</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS</td>
<td>Map-like: FNH</td>
</tr>
<tr>
<td></td>
<td>Irrespective of SAA/CRP</td>
</tr>
<tr>
<td>SAA</td>
<td>Positive: I-HCA</td>
</tr>
<tr>
<td>CRP</td>
<td>Diffuse positive: I-HCA</td>
</tr>
</tbody>
</table>

**Indeterminate:**
- Atypical staining patterns, limited biopsy
- Further management: follow-up vs. repeat bx
  - Morphologic suspicion, additional stains
  - Imaging, clinical setting (size, patient age)
CRP: periseptal staining

FNH
FNH with map-like GS and SAA+
SAA+ in adjacent liver
“FNH-like lesion”: two settings

-Lesions with lack of well-developed features

-Morphology and GS staining similar to classic FNH
  • Adjacent to tumors
  • Cirrhosis
  • Vascular tumors, Budd-Chiari syndrome
Metastatic adenocarcinoma

FNH-like
## Practical considerations: summary

<table>
<thead>
<tr>
<th>Diagnostic Challenge</th>
<th>Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-HCA and FNH: overlapping features</td>
<td>Essential stains: GS, SAA Others, if required</td>
</tr>
<tr>
<td>GS, SAA interpretation</td>
<td>Map-like GS: FNH SAA/CRP can be focally positive in FNH</td>
</tr>
<tr>
<td>SAA, CRP positive in adjacent liver</td>
<td>Focus on morphology Obtain CD34 stain</td>
</tr>
<tr>
<td>FNH-like</td>
<td>Adjacent to other masses Vascular tumors/malformations Vascular diseases (Budd-Chiari syndrome)</td>
</tr>
</tbody>
</table>

- GS: Glomerular Storage
- SAA: Sorbitol Storage
- CRP: Carbohydrate Recognition Protein
β-catenin-activated hepatocellular neoplasms

• Association with HCC
  Frequent cytologic atypia
  Frequent loss of reticulin
• Cytogenetic changes like HCC

Zucman-Rossi, Hepatol 2006
Bioulac-Sage, Hepatol 2007
Evason/Kakar, Hum Pathol 2013
**β-catenin-activated hepatocellular neoplasms**

<table>
<thead>
<tr>
<th>HCA</th>
<th>HNF1α</th>
<th>Inflammatory</th>
<th>Unclassified</th>
</tr>
</thead>
</table>

- Atypical
- HCC

**β-catenin activation**
Inflammatory HCA with β-catenin activation

• 10% of cases
• High risk feature

GS: diffuse
SAA positive
Wnt signaling pathway

Gonzalez, Hepatol, 2006
Hepatocellular neoplasm with exon 3 β-catenin mutation

-Nuclear translocation of β-catenin
β-catenin activation

• β-catenin mutation present
  70% HCC: nuclear β-catenin
  20% adenomas/atypical: nuclear β-catenin
• Diffuse GS staining
  Better correlates with β-catenin activation

Hale/Kakar, Mod Pathol 2016
Bioulac-Sage, Hepatol 2007
β-catenin mutated

- No nuclear β-catenin
- Diffuse GS

β-catenin: membranous

GS: diffuse
Interpretation of GS staining

- Spectrum of histologic patterns
- Definition and pitfalls in interpretation of diffuse GS
GS patterns in adenoma

- Perivascular and patchy
- Expanded perivascular
- Diffuse
Definition of ‘diffuse’ GS staining:

“Positive cytoplasmic overexpression, homogeneous or heterogeneous, but on >50% of tumor”

Patchy: Less than 50%

Zucman-Rossi, Oncol, 2007
Bioulac-Sage, Hepatology, 2007
Diffuse homogeneous
GS ~100%

Diffuse heterogeneous
GS >50%
GS: diffuse heterogeneous (≥50%) vs. patchy staining (<50%)
Diffuse GS $\geq 50\%$

$<50\%$ or $\geq 50\%$
<table>
<thead>
<tr>
<th>Staining pattern</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse homogeneous</td>
<td>Moderate to strong cytoplasmic staining &gt;90% of lesional cells</td>
</tr>
<tr>
<td></td>
<td>Likely β-catenin activation</td>
</tr>
<tr>
<td>Diffuse heterogeneous</td>
<td>Moderate to strong cytoplasmic staining in 50-90% of lesional cells</td>
</tr>
<tr>
<td></td>
<td>Lower association with β-catenin activation</td>
</tr>
<tr>
<td>Patchy (not diffuse)</td>
<td>β-catenin activation very unlikely</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>Indefinite for β-catenin activation</td>
</tr>
</tbody>
</table>
β-catenin-activated hepatocellular neoplasms

HCA

HNF1α  Inflammatory  Unclassified

Atypical

β-catenin activation

HCC
# Atypical features

## Clinical
- Male gender (any age)
- Age (>50 years)
- Glycogen storage diseases, androgen use

## Morphologic
- Focal cytologic atypia
- Focal reticulin loss
- Nuclear β-catenin, diffuse GS

Bedossa, Hum Pathol 2014
Diffuse GS

Nuclear β-catenin
HCC: reticulin loss
Inflammatory HCA

SAA
Diagnosis: Atypical hepatocellular neoplasm (AHN)

Diffuse GS: β-catenin activation
No other high risk feature
Terminology

• Atypical hepatocellular neoplasm
• Well-differentiated hepatocellular neoplasm with atypical/borderline features
• Atypical adenoma
Hepatocellular neoplasm with uncertain malignant potential (HUMP)

Hepatocellular neoplasm with atypical characteristics (HONC)
Are you a HUMPPer or a HONCer?

HUMP: Hepatocellular neoplasm with uncertain malignant potential
HONC: Hepatocellular neoplasm with atypical characteristics

| Clinical                                      | Male gender (any age)                      |
|                                               | Age (>50 years)                            |
|                                               | *Glycogen storage diseases, androgen use* |
| Morphologic                                  | Focal cytologic atypia                     |
|                                               | Focal reticulin loss                       |
|                                               | Nuclear β-catenin , diffuse GS             |
Ancillary studies

- HSP70, Glypican-3
- β-catenin mutation analysis
- TERT promoter mutation
- Cytogenetic changes: Gains of 1, 7, 8

Hale/Kakar, USCAP 2015
Pilati, Cancer Cell 2014
Evason/Kakar, Hum Pathol 2013
HSP70
• Maybe helpful in a small minority of atypical lesions
• Diffuse strong staining

Lagana, Appl Immunohistochem Mol Morph, 2012
Nguyen/Kakar, Mod Pathol 2015
HSP70: diffuse nuclear staining
Ancillary studies

- HSP70, Glypican-3
- Sequencing:
  - β-catenin mutation: exon 3, others (exon 7,8)
  - APC, AXIN mutations
- TERT promoter mutation
- Cytogenetic changes: Gains of 1, 7, 8

Hale/Kakar, USCAP 2015
Pilati, Cancer Cell 2014
Evason/Kakar, Hum Pathol 2013
Atypical hepatocellular adenoma–like neoplasms with β-catenin activation show cytogenetic alterations similar to well-differentiated hepatocellular carcinomas

Kimberley J. Evasion MD, PhD, James P. Grenert MD, PhD, Linda D. Ferrell MD, Sanjay Kakar MD

Human Pathology (2013) 44, 750–758

FISH by JP Grenert, UCSF
## Recommendations

No map-like GS typical of FNH  
Cytoarchitectural atypia not enough for HCC

<table>
<thead>
<tr>
<th>Biopsy</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>-Woman</td>
<td>Hepatocellular adenoma</td>
</tr>
<tr>
<td>-No high risk feature</td>
<td></td>
</tr>
<tr>
<td><strong>High risk features</strong></td>
<td></td>
</tr>
<tr>
<td>-Man (any age)</td>
<td>Atypical hepatocellular neoplasm (AHN)</td>
</tr>
<tr>
<td>-Age &gt;50 years</td>
<td>-Reason for AHN can be stated in a comment</td>
</tr>
<tr>
<td>-Focal atypical features insufficient for HCC</td>
<td>-Other terms like HUMP</td>
</tr>
<tr>
<td>-β-catenin activation</td>
<td></td>
</tr>
</tbody>
</table>
### Recommendations

No map-like GS typical of FNH

Cytoarchitectural atypia not enough for HCC

<table>
<thead>
<tr>
<th>Resection</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>-Woman</td>
<td>Hepatocellular adenoma</td>
</tr>
<tr>
<td>-No high risk feature</td>
<td></td>
</tr>
<tr>
<td>-Man (any age)</td>
<td>Hepatocellular adenoma</td>
</tr>
<tr>
<td>-Age &gt;50 years</td>
<td>(can recommend follow-up, as HCA are uncommon in this setting)</td>
</tr>
<tr>
<td>-No other risk factor</td>
<td></td>
</tr>
</tbody>
</table>

Focal atypical features insufficient for HCC

HCA or AHN

Depends on extent of atypia on resection

β-catenin activation

β-catenin HCA (WHO 2010), or AHN with β-catenin activation
Recommendations

HCC
• Cytoarchitectural abnormalities
• Multifocal reticulin loss
• Do not use AHN in this setting
## Management of HCA

<table>
<thead>
<tr>
<th>Management</th>
<th>Tumor characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conservative with annual surveillance</td>
<td>Solitary HCA, &lt;5 cm</td>
</tr>
<tr>
<td></td>
<td>No high risk features</td>
</tr>
<tr>
<td>Resection</td>
<td>Women: solitary HCA ≥5 cm</td>
</tr>
<tr>
<td></td>
<td>Men (?women&gt;50 years): all cases</td>
</tr>
<tr>
<td></td>
<td>High-risk features</td>
</tr>
</tbody>
</table>
IHC: subtyping adenoma

• Subtyping adenoma not necessary if β-catenin activation excluded

• Establish diagnosis of adenoma based on morphology, not by IHC used for subtyping

• Pitfalls
  - LFABP loss can occur in HCC
  - SAA, CRP staining can be seen in HCC
  - Diffuse GS staining in HCC
LFABP loss in HCC

Cho/Gill, Hum Pathol 2016
Hepatic adenomatosis

• By definition, >10 adenomas
• Young women
• Most are HNF1α-inactivated or inflammatory
• Pathogenesis
  Obesity, less strong association with OCs
  Germline *HNF1α* mutations
• Glycogen storage disease type I, III
34/M, 4.5 cm liver mass
Minimal atypia
Reticulin loss
Atypical features

- Cytoarchitectural abnormalities
- Extensive loss of reticulin

Atypical hepatocellular neoplasm, or HCC
Summary

<table>
<thead>
<tr>
<th>Biopsy diagnosis</th>
<th>Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FNH vs HCA</strong></td>
<td>Resection vs no resection</td>
</tr>
<tr>
<td></td>
<td>Minimum stains: GS, SAA</td>
</tr>
<tr>
<td><strong>Hepatocellular tumors</strong></td>
<td>Resection recommended</td>
</tr>
<tr>
<td>Men, size ≥5 cm</td>
<td>-Risk of bleeding</td>
</tr>
<tr>
<td>FNH excluded</td>
<td>-Risk of HCC</td>
</tr>
<tr>
<td></td>
<td>Distinction between HCA, AHN and HCC on bx may not be important</td>
</tr>
<tr>
<td><strong>Hepatocellular tumors</strong></td>
<td>HCA vs AHN/HCC necessary</td>
</tr>
<tr>
<td>Woman, size &lt;5 cm</td>
<td>Multiple: dictated by size of largest nodule</td>
</tr>
<tr>
<td>FNH excluded</td>
<td></td>
</tr>
</tbody>
</table>
40/F, 9 cm liver mass
Most of the tumor: no atypia
8 mm atypical focus
Pseudoacinar, small cell change
Reticulin stain
Atypical features

- Cytoarchitectural abnormalities
- Abnormal reticulin pattern

Atypical hepatocellular neoplasm, or HCC arising in HCA
## Summary

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<tr>
<td>Hepatocellular tumors</td>
<td>Resection recommended</td>
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<td>Men, size $\geq 5$ cm</td>
<td>- Risk of bleeding</td>
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<tr>
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<td></td>
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</tr>
<tr>
<td>Woman, size $&lt;5$ cm</td>
<td>Multiple: dictated by size of largest nodule</td>
</tr>
<tr>
<td>FNH excluded</td>
<td></td>
</tr>
<tr>
<td>Stain</td>
<td>Interpretation</td>
</tr>
<tr>
<td>----------</td>
<td>-------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Reticulin</td>
<td>Loss: HCC</td>
</tr>
<tr>
<td>GS</td>
<td>Diffuse: Suggest β-catenin activation Map-like: FNH Patchy, no specific pattern: HCA</td>
</tr>
<tr>
<td>SAA</td>
<td>Inflammatory HCA</td>
</tr>
</tbody>
</table>
### H-HCA: diagnostic challenges

<table>
<thead>
<tr>
<th>Diagnostic challenge</th>
<th>Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat may be absent</td>
<td>Overall morphologic features LFABP, other stains</td>
</tr>
<tr>
<td>Fat in other HCA subtypes, FNH</td>
<td>Overall morphologic features LFABP, other stains</td>
</tr>
<tr>
<td>LFABP can be weak</td>
<td>Titrate stain appropriately ‘All or none’: any +ve staining usually means LFABP retained</td>
</tr>
<tr>
<td>LFABP loss in HCC</td>
<td>LFABP is used to subtype HCA Should not be used to diagnose HCA</td>
</tr>
</tbody>
</table>
H-HCA without fat
Unclear situations

Small (<5 cm) tumors

• Atypical clinical setting, no atypical morphologic features

• Borderline GS staining pattern

Atypical neoplasm extending to margin
# Management of HCA

<table>
<thead>
<tr>
<th>Management</th>
<th>Tumor characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conservative with annual surveillance</td>
<td>Solitary HCA &lt;5 cm</td>
</tr>
<tr>
<td>Resection</td>
<td>Women: solitary HCA ≥5 cm</td>
</tr>
<tr>
<td></td>
<td>Men (women &gt;50 years): all cases</td>
</tr>
<tr>
<td></td>
<td>High-risk features</td>
</tr>
</tbody>
</table>
## HCA subtypes: US and Europe

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Bioulac-Sage, Hepatol, 2007 (n=93)</th>
<th>Shafizadeh/Kakar, Hum Path 2014 (n=28)</th>
<th>Thung, EASL 2013 (n=61)</th>
<th>Bioulac-Sage, AJSP 2012 (n=137)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HNF1α</td>
<td>33%</td>
<td>29%</td>
<td>33%</td>
<td>22%</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>40%</td>
<td>32%</td>
<td>44%</td>
<td>53%</td>
</tr>
<tr>
<td>β-catenin, not IHCA</td>
<td><strong>17%</strong></td>
<td>0</td>
<td><strong>2%</strong></td>
<td><strong>2%</strong></td>
</tr>
<tr>
<td>IHCA with β-catenin</td>
<td>2%</td>
<td>3%</td>
<td>2%</td>
<td>11%</td>
</tr>
<tr>
<td>Unclassified</td>
<td>8%</td>
<td>36%</td>
<td>16%</td>
<td>13%</td>
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Shafizadeh/Kakar, Hum Pathol 2014
# Imaging features

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<th>FNH</th>
<th>Inflammatory HCA</th>
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<tr>
<td>Central scar</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Contrast CT enhancement</td>
<td>Early homogenous</td>
<td>Heterogeneous and persistent</td>
</tr>
<tr>
<td>MRI T1-weighted</td>
<td>Hypointense</td>
<td>Hyperintensity</td>
</tr>
<tr>
<td>MRI T2-weighted</td>
<td>Hypointense</td>
<td>Strong hyperintensity</td>
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<td>Morphology like I-HCA, SAA negative</td>
<td>SAA negative in 5-10% Most are CRP-positive</td>
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<td>CRP specificity is low FNH often positive in periseptal region</td>
<td>Overall morphologic features Other stains: SAA, GS</td>
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<tr>
<td><strong>SAA, CRP positive in adjacent liver</strong></td>
<td>Focus on morphology Obtain CD34 stain</td>
</tr>
<tr>
<td>I-HCA with diffuse GS staining</td>
<td>10% of cases Considered as high-risk HCA</td>
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<td>Overlap with FNH</td>
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HCC: criteria for diagnosis

Two criteria

- Cytoarchitectural abnormalities
  - Small cell change/cytologic atypia
  - Thick cell plates
  - Prominent pseudoacinar architecture

- Multifocal reticulin loss
  (not necessary if sufficient cytoarchitectural atypia)
62/F, 6 cm liver mass
Nuclear atypia, no architectural changes
Normal liver: perivenular glutamine synthetase (GS)

β-catenin-activation: diffuse GS